General

Guideline Title

Guidelines on the investigation and management of antiphospholipid syndrome.

Bibliographic Source(s)

Keeling D, Mackie I, Moore GW, Greer IA, Greaves M, British Committee for Standards in Haematology. Guidelines on the investigation and management of antiphospholipid syndrome. Br J Haematol. 2012 Apr;157(1):47â€“58. [122 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Greaves M, Cohen H, MacHin SJ, Mackie I. Guidelines on the investigation and management of the antiphospholipid syndrome. Br J Haematol. 2000 Jun;109(4):704-15.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (A-C) and strength of recommendation (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

Detection of Antiphospholipid Antibodies (aPL) in the Clinical Laboratory

Lupus Anticoagulant Testing

- The dilute Russell viper venom time (DRVVT) and one other test should be employed for lupus anticoagulant (LA) detection (2C), and the patient regarded as having a LA if either test is positive.
- A confirmatory step (e.g., using a high phospholipid concentration, platelet neutralizing reagent or LA-insensitive reagent) is needed to demonstrate phospholipid dependence (1A).

Solid Phase aPL Assays

- When testing for aPL is indicated, testing for LA and for immunoglobulin G (IgG) antibodies to β_2–glycoprotein I (β_2GPI) should be performed. The latter can be detected either by an IgG anticardiolipin antibodies (aCL) enzyme-linked immunosorbent assay (ELISA) or an IgG anti-β_2GPI ELISA (2C). An aCL ELISA may detect antibodies to other phospholipid binding proteins as well as anti-β_2GPI.
- In patients with thrombosis, measuring immunoglobulin M (IgM) antibodies does not add useful information (2B).
- In patients with pregnancy morbidity, the role of IgM antibodies is unclear (2C).

- Testing for immunoglobulin (IgA) antibodies is not recommended (1B).
- When assessing clinical significance account should be taken of whether the patient has LA, aCL/anti-β_2GPI, or both and of the isotype and titre in the solid phase tests (1B).

Who Should Be Tested for aPL and How Should This Affect Management of Patients

Incidental Finding of aPL

- The guideline authors recommend that primary thromboprophylaxis should not be used in those incidentally found to have aPL (2B).

Which Patients with Venous Thrombosis Should Be Tested for aPL and How Should the Result Affect Management?

- The guideline authors recommend testing for aPL in patients with unprovoked proximal deep vein thrombosis (DVT) or pulmonary embolism (PE) after stopping anticoagulation (for at least 7 days) as the presence of aPL will influence the balance of risks and benefits and support long-term anticoagulant therapy (2B).

Which Patients with Ischaemic Stroke Should Be Tested for aPL and How Should the Result Affect Management?

- Routine screening for aPL in patients with ischaemic stroke is not warranted (1B).
- Young adults (<50 years) with ischaemic stroke should be screened for aPL (2C).
- For unselected stroke patients with a single positive aPL test result, antiplatelet therapy and warfarin are equally effective for preventing recurrent stroke (1B) and antiplatelet therapy is preferred on grounds of convenience.
- Young adults (<50 years) with ischaemic stroke and antiphospholipid syndrome (APS) may be at high risk of recurrence and cohort studies suggest that anticoagulation with warfarin should be considered, but there is no strong evidence that it is better than antiplatelet therapy (2C).

Anticoagulation in APS

- The target international normalized ratio (INR) for vitamin K antagonist (VKA) therapy in APS should normally be 2.5 (target range 2.0–3.0) (1A).

Monitoring Oral Anticoagulants in Patients with a Lupus Anticoagulant

- A baseline prothrombin time (PT) should be performed; if this is prolonged, an alternative PT reagent for which the baseline is normal should be used (1C).
- If there are problems identifying a suitable PT system for VKA control, the use of an amidolytic factor X (FX) assay could be considered (2C).

Which Patients with Obstetric Complications Should Be Tested for aPL and How Should the Result Affect Management?

- Women with recurrent pregnancy loss (≥3 pregnancy losses) before 10 weeks gestation should be screened for aPL (1B).
- For women with APS with recurrent (≥3) pregnancy loss, antenatal administration of heparin combined with low dose aspirin is recommended throughout pregnancy (1B). In general, treatment should begin as soon as pregnancy is confirmed.
- For women with APS and a history of pre-eclampsia or fetal growth restriction (FGR), low dose aspirin is recommended.
- Women with aPL should be considered for post-partum thromboprophylaxis (1B).

Definitions:

Quality of Evidence

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series, or just opinion.

Strength of Recommendations

Strong (grade 1) Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2) Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Antiphospholipid syndrome

Guideline Category

Diagnosis

Management

Prevention

Treatment

Clinical Specialty

Cardiology

Endocrinology

Family Practice

Hematology

Internal Medicine

Nephrology

Neurology

Obstetrics and Gynecology

Preventive Medicine

Pulmonary Medicine

Rheumatology

Intended Users

Advanced Practice Nurses

Clinical Laboratory Personnel

Health Care Providers

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide healthcare professionals with clear guidance on the diagnosis and management of patients with antiphospholipid syndrome (APS)

Target Population

People in the United Kingdom with antiphospholipid syndrome

Interventions and Practices Considered

Diagnosis/Screening

1. Lupus anticoagulant (LA) testing for antiphospholipid syndrome (APS) using the dilute Russell viper venom time (DRVVT) plus one other test
2. Confirmatory LA test using a high phospholipid concentration, platelet neutralizing reagent or LA-insensitive reagent
3. Solid-phase antiphospholipid (aPL) antibodies
    - Enzyme-linked immunosorbent assay (ELISA) for anticardiolipin immunoglobulin G (IgG) antibodies or anti-β2-glycoprotein I IgG antibodies
4. Assessment of isotype and titre in the solid phase tests
5. Discontinuation of anticoagulation prior to aPL testing
6. Screening patients <50 years with ischaemic stroke for aPL (routine screening of all ischemic stroke patients not recommended)
7. Screening of women with ≥3 pregnancy losses for aPL

Note: IgM antibody detection was considered but not recommended for thrombosis (lack of useful information) and pregnancy morbidity (lack of clarity). IgA antibody detection is not recommended.

Management/Treatment/Prevention

1. Antiplatelet therapy (preferred) or warfarin to prevent recurrent stroke
2. Vitamin K antagonism based on international normalized ratio (INR) level
3. Choice of a prothrombin time (PT) reagent that yields normal baseline for patients with LA
4. Use of amidolytic factor X assay if a suitable PT assay is not found
5. Antenatal heparin + low dose aspirin throughout pregnancy for women with ≥3 pregnancy losses
6. Low dose aspirin for women with APS and a history of pre-eclampsia or fetal growth restriction
7. Post-partum thromboprophylaxis for women with aPL

Note: Primary thromboprophylaxis not recommended for patients incidentally found to have aPL.

Major Outcomes Considered

- Sensitivity, specificity, and utility of diagnostic tests
- Incidence of thrombosis and thromboembolism
- Recurrence rate of thrombosis or stroke
- Disability rate
- Mortality

- Incidence of abnormal baseline prothrombin time (PT)
- Change in international normalized ratio (INR)
- Incidence of pregnancy complications including pregnancy loss

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The guidance is updated with reference to relevant publications since 2000. Publications known to the writing group were supplemented with additional papers identified by searching PubMed for publications in the last 11 years using the key words: lupus anticoagulant, anticardiolipin, antiphospholipid, β_2–glycoprotein I, antiprothrombin and limits (clinical trial, randomized control trial, meta-analysis, humans, core clinical journals, English language).

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series, or just opinion.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

The 'GRADE' system (Grading of Recommendations Assessment, Development, and Evaluation) was used to quote levels of evidence, details of which can be found at http://www.bcshguidelines.com/BCSH_PROCESS/EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION/43_GRADE.html (see the "Rating Scheme for Strength of Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

This guidance updates and replaces the previous guideline on the investigation and management of antiphospholipid syndrome (APS) published in 2000, though where there have not been changes the guideline authors refer back to them when appropriate.

The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology (BCSH).

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (grade 1) Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2) Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Cost Analysis

A formal cost analysis was not performed and published analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The guideline was reviewed by a sounding board of approximately 50 UK haematologists, the Royal College of Obstetricians and Gynaecologists (RCOG), and the British Committee for Standards in Haematology (BCSH) Committee and comments incorporated where appropriate.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

General Population

Appropriate diagnosis and management of antiphospholipid syndrome (APS)

Pregnant Women

Reduction in the incidence of recurrent and late pregnancy loss

Potential Harms

Warfarin therapy carries a substantial risk of bleeding. Although the risk is greatest in the first weeks, it persists for the duration of exposure.

Qualifying Statements

Qualifying Statements

- The objective of this guideline is to provide healthcare professionals with clear guidance on the diagnosis and management of patients with antiphospholipid syndrome though individual patient circumstances may dictate an alternative approach.
- While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2000 Jun (revised 2012 Apr)

Guideline Developer(s)

British Committee for Standards in Haematology - Professional Association

Source(s) of Funding

British Committee for Standards in Haematology

Guideline Committee

Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology

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Financial Disclosures/Conflicts of Interest

None of the authors have declared a conflict of interest.

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Guideline Availability

Electronic copies: Available from the British Committee for Standards in Haematology Web site .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was updated by ECRI Institute on July 30, 2012. The information was verified by the guideline developer on September 5, 2012. This summary was updated by ECRI Institute on March 10, 2014 following the U.S. Food and Drug Administration advisory on Low Molecular Weight Heparins.

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